

## LITERATURE REVIEW LEVEL OF EVIDENCE FOR GENDER-AFFIRMING TREATMENTS

### ISSUE:

Health Affairs requested a review of existing research literature on the level of evidence for gender-affirming treatments for gender dysphoria (i.e., behavioral health, hormone therapy, and surgical procedures).

### BACKGROUND:

Systematic reviews are a rigorous way to compile scientific evidence on health care issues like treatment, diagnosis, or prevention, aiming to minimize bias by assessing the methodological quality and overall strength of the studies. In emerging areas of research like transgender health, systematic reviews face limitations (e.g., lack of available research, methodological differences, evolving treatments, lack of research funding) making it difficult to draw clear conclusions on the strength of the evidence.

The levels of evidence hierarchy range from low (expert opinion, case reports, case series), moderate (cohort studies, case-control studies), and high (meta-analyses, systematic reviews, randomized control trials). Higher levels of hierarchy represent strong research evidence due to rigorous study design. Notably, there are little to no randomized controls trials for transgender health due to ethical concerns and methodological challenges.

A total of 34 studies on transgender health and gender-affirming treatments were included, with 30 peer-reviewed systematic reviews, two independent systematic reviews, one electronic health record review, and one follow-up study.

### DISCUSSION:

#### Behavioral Health

Six systematic reviews were included to review the level of evidence on transgender health and treatment. *The strength of the evidence on transgender mental health and gender-affirming care is low to moderate.*

Research findings consistently show high rates of mental health disparities and the benefits of gender-affirming care, but are limited by cross-sectional study designs, reliance on self-reported data, lack of standardized assessments, and small sample sizes. Even with low to moderate research evidence, *a consistent recommendation in the literature is that mental health care should be available before, during, and after transitioning.* The main themes of the systematic reviews on behavioral health include:

#### Mental Health Disparities are Driven by Discrimination and Minority Stress.

- A meta-synthesis of 42 studies found that 55% of transgender individuals experienced suicidal ideation and 29% attempted suicide in their lifetime, with higher ideation rates among transfeminine individuals and higher attempt rates among transmasculine individuals.<sup>i</sup>

- A systematic review of 165 peer-reviewed articles found that transgender individuals are approximately twice as likely to receive a psychiatric diagnosis compared to cisgender individuals, with mood disorders (1.5x higher), anxiety disorders (3.9x higher), and psychotic disorders (3.8x higher) being the most prevalent. Additionally, the suicide attempt rate is estimated to be 13 times higher among transgender individuals compared to their cisgender counterparts. The higher prevalence of mental health disorders was largely driven by minority stress, discrimination, social rejection, lack of access to gender-affirming care, and increased exposure to violence and victimization.<sup>ii</sup>
- The risk of suicide ideation and attempts among transgender individuals increases due to gender identity-related disparities, discrimination, lack of family and social support, barriers to gender-affirming care, co-occurring mental health conditions, economic instability, and experiences of violence or victimization.<sup>iii</sup>
- A systematic review of 15 quantitative studies found that transgender individuals experience high levels of discrimination, prejudice, and bias, leading to negative mental health outcomes (e.g., psychological distress, substance abuse, eating disorders, reduced relationship quality, ineffective coping, lower self-esteem, and a higher risk of attempted suicide).<sup>iv</sup>
- A systematic review of 47 studies found a strong correlation between minority stress and suicidality in transgender and gender non-conforming (TGNC) adults, but the evidence quality is low, as most studies were cross-sectional, relied on self-reported measures, and lacked standardized assessments, making causality difficult to determine.<sup>v</sup>
- A systematic review and meta-analysis of 85 cross-sectional quantitative studies found that transgender and gender-diverse (TGD) individuals experience significantly higher rates of depression, suicidal ideation, and suicide attempts, largely driven by minority stress factors such as discrimination, social rejection, lack of gender-affirming care, and victimization.<sup>vi</sup>

#### Effectiveness and Limitations of Affirmative Psychological Interventions.

- A systematic review of 22 studies found that affirmative psychological interventions for transgender and non-binary (TGNB) adults and adolescents show promising improvements in depression, anxiety, suicidality, self-acceptance, coping skills, and minority stress, but evidence quality remains limited due to methodological inconsistencies, small sample sizes, and high risk of bias across studies.<sup>vii</sup>
- Research demonstrates that suicide risk among transgender and gender-diverse (TGD) individuals is mitigated by access to gender-affirming care, strong social and family support, legal and social recognition, affirming mental health services, community connectedness, and protections against discrimination.<sup>viii</sup>

#### **Gender-Affirming Hormone Therapy (GAHT):**

Twelve systematic reviews were included to review the level of evidence on GAHT. ***The strength of the evidence on the effectiveness of GAHT, for physical and mental health, is generally low to moderate.***

Research findings on GAHT are typically observational, lack randomized controlled trials (RCTs), and have small sample sizes. While literature on GAHT consistently demonstrates improvements in mental health, gender dysphoria, and body composition, its long-term effects on cardiovascular

health and metabolism remain uncertain due to methodological limitations. *Clinical practice guidelines strongly recommend confirming the diagnosis of gender dysphoria, pre-hormone therapy medical evaluations, monitoring bone health, and an individualized approach to GAHT.*<sup>ix</sup> The main themes of the systematic reviews on GAHT include:

#### Cardiovascular, Metabolic, and Bone Density Risks.

- A systematic review of 2 studies – 8 cross-sectional and 4 cohort studies – found that gender-affirming hormone therapy may influence the risk of subclinical atherosclerosis (i.e., plaque builds up inside the arteries) among transgender men, with the evidence being moderate. However, the effects on cardiovascular health for transgender women may be neutral or even beneficial.<sup>x</sup>
- The systematic review by Connelly et al. (2021) included 14 studies encompassing a total of 1,309 transgender individuals (approximately equal numbers of transgender men and women) treated with GAHT between 1989 and 2019. Due to methodological limitations, the authors concluded that there is insufficient data to advise the impact of GAHT on blood pressure.<sup>xi</sup>
- The systematic review by Kotamarti et al. (2021) analyzed 27 studies, encompassing 10,428 transgender patients undergoing GAHT. The findings revealed that transgender women had a higher incidence of venous thromboembolism compared to transgender men, but the strength of the evidence was moderate.<sup>xii</sup>
- While the quality of evidence is low, it is strongly recommended that monitoring of bone mineral density occur during GAHT, especially for transgender individuals at risk of osteoporosis or who have discontinued GAHT after gonadectomy.<sup>xiii</sup>

#### Psychological Benefits.

- The Endocrine Society's clinical practice guidelines are based on evidence from two systematic reviews, as well as the best available evidence from other published systematic reviews and individual studies. The guidelines strongly support GAHT for improving psychological well-being and reducing gender dysphoria; however, it acknowledges gaps in long-term safety data, the need for more standardized research, and the lack of high-quality evidence on optimal hormone regimens and monitoring strategies.<sup>xiv</sup>
- One systematic review of seven observational studies, with a total of 552 transgender participants, found that GAHT was associated with improvements in quality of life, depression, and anxiety; but the evidence quality was very low to low.<sup>xv</sup>
- A systematic review by Baker et al. (2021) included 20 studies reported in 22 publications. Findings demonstrated that gender-affirming hormone therapy (GAHT) is associated with improved mental health and quality of life, but the strength of evidence was low due to small sample sizes, high risk of bias in study designs, and confounding factors such as concurrent gender-affirming surgeries.<sup>xvi</sup>
- A systematic review of 46 studies found that GAHT reduces psychological distress and depressive symptoms, but the evidence quality among studies was highly variable.<sup>xvii</sup>
- A systematic review of 38 studies found that GAHT reduces gender dysphoria and improves psychological well-being and quality of life, but the overall evidence quality is low to moderate.<sup>xviii</sup>
- The systematic review by Hughto and Reisner (2016) included three uncontrolled prospective cohort studies with a total of 247 transgender adults. Results found that GAHT

was associated with improved psychological functioning and quality of life, but the evidence is low.<sup>xix</sup>

#### Effectiveness and Limitations of GAHT.

- Endocrine Society's clinical practice guidelines are based on evidence from two systematic reviews, as well as the best available evidence from other published systematic reviews and individual studies. Most evidence levels were low or very low, except for hormone monitoring and cardiovascular risk assessment, which had moderate-quality evidence. The guidelines strongly support GAHT for improving psychological well-being and reducing gender dysphoria; however, it acknowledges gaps in long-term safety data, the need for more standardized research, and the lack of high-quality evidence on optimal hormone regimens and monitoring strategies.<sup>xx</sup>
- One narrative systematic review on four retrospective studies found that antiandrogens (e.g., cyproterone acetate, leuprolide, and spironolactone) effectively suppress testosterone levels in transgender women, but there is insufficient evidence comparing their impact on feminization outcomes like breast development, body fat redistribution, and facial/body hair reduction.<sup>xxi</sup>
- A systematic review found that gender-affirming hormone therapy (GAHT) has mixed effects on sexual function, with testosterone in transgender men generally increasing libido but sometimes reducing genital sensitivity, while estrogen in transgender women often decreases spontaneous erections and libido, though satisfaction improves with gender congruence.<sup>xxii</sup>
- The systematic review by Spanos et al. (2020) included 26 studies and found that GAHT is effective in altering body composition. Testosterone therapy in transgender men increased lean mass, decreased fat mass, and had no significant impact on insulin resistance, while estrogen therapy in transgender women led to decreased lean mass, increased fat mass, and may worsen insulin resistance. However, the overall strength of evidence was moderate to low largely due to a lack of long-term data.<sup>xxiii</sup>

#### Gender-Affirming Surgery (GAS)

Fifteen systematic reviews, one follow-up study, and one database study were included to review the level of evidence on GAS. ***The strength of the evidence on the effectiveness of GAS are generally low to moderate.***

The literature review highlights that GAS is associated with high patient satisfaction, reduced gender dysphoria, and improvements in mental health, including decreased anxiety, depression, and suicidality. While complication rates for top surgeries and facial feminization are relatively low, genital surgeries such as phalloplasty and vaginoplasty present higher risks. Despite these challenges, long-term studies show that regret rates are extremely low, with most individuals reporting improved quality of life, body image satisfaction, and overall well-being. ***The research recommends standardized assessment tools, long-term follow-up, and higher-quality research to determine the long-term safety and effectiveness of GAS procedures.*** The main themes of the systematic reviews on GAS include:

### Patient Satisfaction and Quality of Life.

- A narrative review of current research concluded that GAS decrease rates of gender dysphoria, depression, and suicidality, and significantly improve quality-of-life measures. However, the strength of the evidence is moderate due to inconsistent approaches in measuring post-operative behavioral health impacts.<sup>xxiv</sup>
- The Hayes 2018 and 2020 independent reports<sup>1</sup> on GAS found that while transgender individuals typically experienced high satisfaction, reduced gender dysphoria symptoms and improved body image satisfaction, the overall quality of evidence is low. Across the two reports, findings showed persistent limitations such as small sample sizes, lack of control groups, and short follow-up periods.<sup>xxv, xxvi</sup>
- A systematic review of 79 studies found GAS to be associated with high levels of surgical satisfaction and improved quality of life for transgender individuals at least one-year post-surgery. Additionally, the majority of patients reported reduced gender dysphoria, increased body satisfaction, and overall psychological well-being. However, due to methodological limitations, the evidence strength was low to moderate.<sup>xxvii</sup>
- The systematic reviews by Oles et al. (2022) found that GAS, including chest masculinization, breast augmentation, facial feminization, voice surgery and genitoplasty (vaginoplasty, phalloplasty, metoidioplasty, and oophorectomy/colpectomy), generally had high patient satisfaction rates but the strength of the evidence is moderate.<sup>xxviii, xxix</sup>
- A 40-year follow-up study with 15 participants found that patient satisfaction with GAS remained high, with improved body congruency, reduced gender dysphoria, and persistent mental health benefits, including lower rates of suicidal ideation and depression. Despite high complication rates for some procedures (i.e., phalloplasty and vaginoplasty), none of the participants expressed regret.<sup>xxx</sup>
- A systematic review of 54 studies found reduced suicide attempts, anxiety, depression, and gender dysphoria, as well as higher levels of life satisfaction and happiness. However, the strength of the evidence was moderate due to methodological differences.<sup>xxxi</sup>
- The systematic review by Wernick et al. (2019) included 33 studies and found that GAS (i.e., facial feminization or masculinization, vocal feminization, breast augmentation, mastectomy, chest reconstruction, metoidioplasty, orchiectomy, salpingo-oophorectomy, vaginoplasty, or phalloplasty) often led to significant improvements in quality of life, body image/satisfaction, and overall psychiatric functioning.” However, predictive conclusions cannot be drawn due to methodological variability.<sup>xxxii</sup>

### Risks and Complications.

- A narrative review of current research concluded that complication rates for gender-affirming mastectomy and breast augmentation are very low, while those for genital surgeries are also reasonably low.<sup>xxxiii</sup>
- The systematic review and meta-analysis by Ding et al. (2023) included 27 studies comprising a total of 3,388 transgender women who underwent penile inversion vaginoplasty. Results found that the risks were low, but notable, for urinary complications (e.g., incontinence, urethral strictures) and emphasized the importance of postoperative follow-up.<sup>xxxiv</sup>

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<sup>1</sup> The Hayes reports are independently produced and were not located in peer-reviewed journals.

- A systematic review of 21 studies highlighted the increased risk for surgical complications among transgender men undergoing phalloplasty and metoidioplasty, but the strength of the evidence was low to moderate due to the literature consisting of mostly observational or retrospective studies.<sup>xxxv</sup>
- The evidence on the impact of GAS on sexual function is low to moderate quality. Research revealed mixed effects on sexual function, with many transgender individuals reporting improved body image and satisfaction, but also a notable prevalence of sexual dysfunction, including reduced genital sensitivity and orgasmic difficulties, particularly after vaginoplasty and phalloplasty.<sup>xxxvi</sup>
- One study reviewed a database of 4,114 patients who underwent GAS and found that in four years (2015-2019), GAS increased by 400%, with masculinizing procedures being the most common. An overall GAS complication rate was 6%, with bottom surgeries having the highest complication rate at 8%, which was influenced by factors like age and body mass index.<sup>xxxvii</sup>

#### Surgical Regret.

- A systematic review and meta-analysis of 7,928 transgender individuals found an extremely low prevalence of regret (1%) after GAS, with minor regret being more common. Notably, transfeminine surgeries (e.g., vaginoplasty) had a slightly higher regret rate (1%) compared to transmasculine surgeries (e.g., phalloplasty and mastectomy, <1%), though overall regret rates remained extremely low.<sup>xxxviii</sup>
- Another systematic review of 29 studies found that regret rates for GAS were extremely low (1.94%), but the evidence was limited by retrospective study designs. Vaginoplasty had the highest regret rate (4.0%) among transfeminine individuals, while phalloplasty had a notable regret rate among transmasculine individuals, though lower overall (0.8%).<sup>xxxix</sup>
- A systematic review found regret rates for GAS are significantly lower (<1%) compared to elective surgeries among cisgender individuals (0%-47.1% for breast reconstruction, 5.1%-9.1% for breast augmentation, and 10.82%-33.3% for body contouring).<sup>xl</sup>

#### **Summary**

While systematic reviews and meta-analyses provide valuable insights, methodological inconsistencies, high risk of bias, and a scarcity of longitudinal, randomized controlled trials weaken the ability to draw definitive causal conclusions. The strength of the evidence reviewed was:

- Low to moderate for mental health treatment among six systematic reviews.
- Low to moderate on GAHT among twelve systematic reviews.
- Low to moderate for GAS among fifteen systematic reviews.

Notably, there is sufficient research evidence that indicates barriers to accessing gender-affirming care and discrimination are key contributors to healthcare disparities and worsened mental health outcomes for transgender individuals. More high-quality, long-term research is needed to strengthen the evidence base and guide best practices in transgender healthcare.



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